

REMARKS

Upon entry of the present amendment, claims 1, 8-15 and 29 are pending in the above-referenced patent application and are currently under examination. Claim 1 has been amended. Claims 2-7 and 16-28 have been canceled. Claim 29 has been added. Reconsideration of the application is respectfully requested.

Claim 1 has been amended to recite that R⁵ is OH and that “when R⁹ and R¹⁰ are both other than acyl, R⁶ is OP(O)(OR¹⁴)(OR¹⁴).” Support for the amendments to the claim can be found throughout the specification.

New claim 29 recites a preferred compound of the present invention. Support for new claim 29 can be found in the specification at Example 4r.

Applicants believe the claim amendments add no new matter to the claims.

Applicants thank the Examiner for his time and consideration during the telephonic interview of February 4, 2009. Applicants and Examiner discussed the anticipation rejection and the generic formula relied upon for the anticipation rejection. The Examiner agreed that the amendments to claim 1 overcome the anticipation rejection.

I. ANTICIPATION REJECTION OVER SKULNICK

Claim 1 has been rejected under 35 USC § 102(b) as allegedly being anticipated by Skulnick. Applicants respectfully traverse the rejections in view of the comments below.

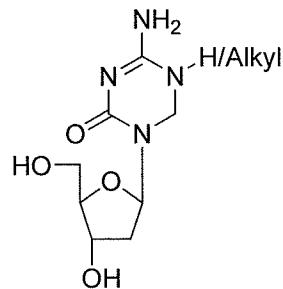
A claim is considered to be anticipated under 35 USC § 102(b) if “the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.” In order for a claim to be anticipated by a reference, the reference must expressly or inherently teach every element of the claim (MPEP § 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Furthermore, for an anticipation rejection to have been proper, the prior art reference

[M]ust clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound **without any need for picking, choosing, and combining various disclosures** not directly related to each other by the teachings of the cited reference. (*In re Arkley*, 455 F.2d 586, 587, 172 USPQ 524, 526 (CCPA 1972), emphasis added).

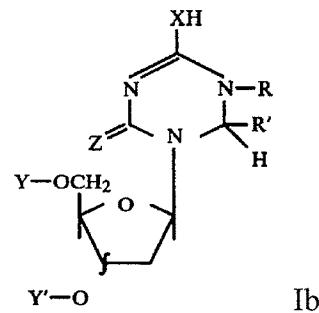
As discussed in detail below, the presently claimed invention is not anticipated in view of Skulnick as Skulnick fails to teach every element set forth in the claims of the instant invention.

The Examiner alleges that Skulnick describes a compound that anticipates the structure of claim 1 of the present invention. Applicants disagree. Applicants note that claim 1 has been amended to recite that “when R⁹ and R¹⁰ are both other than acyl, R⁶ is OP(O)(OR¹⁴)(OR¹⁴).” Thus, compounds such as the following are excluded from amended claim 1 because R⁹ and R¹⁰ are not acyl, and R⁶ is not OP(O)(OR¹⁴)(OR¹⁴):

Compounds excluded from amended claim 1:



Turning to the compounds of Skulnick, the Examiner points to generic formula Ib in column 2, lines 20-69 of Skulnick as allegedly anticipating the instant claims:



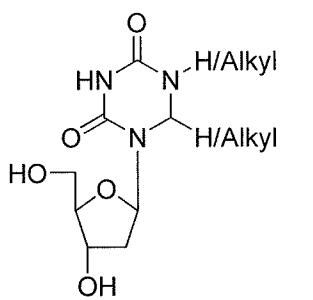
wherein Y is H or phosphono, Y' is H, X is NH or N-alkyl, Z is O, R is H or C2-C4 alkyl and R' is H. In order to arrive at the compounds of the present invention, the Examiner has relied not on a single, disclosed compound that describes all the elements of the claim, as required under *Verdegaal Bros.* Rather, the Examiner has relied on a compound *generic*, and picked those substituents from a large selection of substituents, such that when put together with formula Ib, form a compound that is allegedly encompassed by the claims.

Applicants appreciate that anticipation by a generic formula is appropriate in certain circumstances. As set forth in MPEP § 2131.02, anticipation of a species by a general formula is allowed “if the classes of substituents are sufficiently limited or well delineated” citing *Ex Parte A*, 17 USPQ2d 1716 (BPAI 1990) (internal quotations omitted). In *In re Petering*, 301 F.2d 676, 133 USPQ

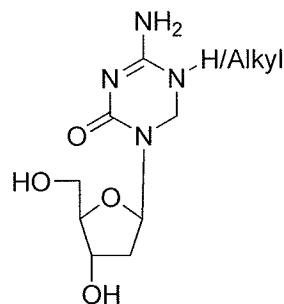
275 (CCPA 1962), the generic formula in the prior art reference encompassed about 20 compounds, such that any of the compounds of the generic formula could be “at once envisaged.”

Unlike in *Petering*, the generic formula of Skulnick that the Examiner relies on describes *thousands* of compounds rather than just the 20 of *Petering*. The generic formula Ib of Skulnick describes at least 6 radicals, each radical including 2 to 7 substituents, where some of the substituents, such as “loweralkyl” and “carboxacyl of from 1 through 18 carbon atoms” include many more substituents. Given the large number of radicals and substituents for the generic formula of Skulnick, there are thousands of compounds encompassed by the generic formula of Skulnick, rather than the 20 compounds of *Petering* that could be “at once envisaged.” As such, Applicants submit that the generic of Skulnick that the Examiner has relied on is much broader than the scope in the generic of *Petering* and cannot be relied upon to anticipate the amended claims of the present invention.

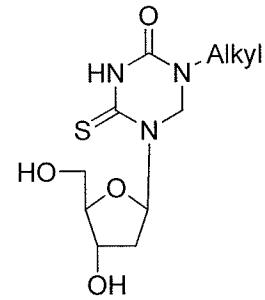
While formula Ib of Skulnick is not sufficient to rely on for an anticipation rejection, Applicants note that the Examples, such as Example 4, describe many specific compounds that would be appropriate to support an anticipation rejection, if such compounds fell within the scope of the amended claims. Applicants note that the compounds of the Examples in Skulnick are described by the following generic structures:



2,4-dione



2-oxo-4-amino



2-thiocarbonyl-4-oxo

As is readily apparent, the compounds in the Examples of Skulnick are not encompassed by the amended claims. For example, the 2,4-dione compounds are outside the scope of the amended claims because claim 1 is drawn to a 2-oxo-4-amino nucleobase structure, not a 2,4-dione structure. The 2-oxo-4-amino compounds of Skulnick, shown here in a tautomeric form of the compounds of Example 4, are also not encompassed by the scope of amended claim 1 because amended claim 1 requires that when R⁹ and R¹⁰ (N⁴ position) are both H, then R⁶ (5-OH) is OP(O)(OR¹⁴)(OR¹⁴). However, R⁶ is H (5'-OH) in the Examples of Skulnick. As discussed above, compounds where R⁶, R⁹ and R¹⁰ are all hydrogen, which includes the 2-oxo-4-amino compounds of Skulnick, are excluded from the amended claims. In addition, the 2-thiocarbonyl-4-oxo compounds of Skulnick are not encompassed by amended claim 1

because there is no thiocarbonyl at the 2 position and no carbonyl at the 4 position of the compounds of amended claim 1. Accordingly, even if the Examiner had pointed to a specific compound of Skulnick in support of the anticipation rejection, Applicants note that the amended claims would still not be anticipated by Skulnick because none of the compounds of the Examples in Skulnick are encompassed by the amended claims.

Accordingly, the compounds of the amended claims are not anticipated under 35 U.S.C. § 102(b) by the generic structure, or any of the compounds in the Examples, of Skulnick. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

II. OBVIOUSNESS REJECTION OVER SKULNICK

While the Examiner has not set forth an obviousness rejection to the pending claims in view of Skulnick alone, Applicants submit that should the Examiner set forth an obviousness rejection over Skulnick alone, the pending claims are also not obvious in view of Skulnick because there is no motivation provided by Skulnick to select the radicals of formula Ib necessary to arrive at the compounds of the present invention.

A claim is considered obvious “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains” (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.

It is well established that a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness for a claimed species or genus (MPEP § 2144.08, citing *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)):

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.

In fact, the Federal Circuit has “decline[d] to extract from *Merck [& Co. v. Biocraft Labs. Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that ... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it.” *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). Thus, it is not enough that the prior art genus describes

all the components of the claimed genus, rather, the Examiner must provide the *motivation* why one of ordinary skill in the art would select the claimed species or genus:

[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound. *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1357, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007). (Emphasis added.)

Accordingly, the Examiner *must* point to some motivation in the reference to modify the known compound and arrive at the claimed compound or genus.

In determining whether there is sufficient motivation to modify the prior art genus, MPEP § 2144.08 provides several factors to be considered by the Examiner:

- the size of the prior art genus
- express teachings by the reference of a particular reason to select the claimed genus
- teachings of structural similarity, including the number of variables which must be selected or modified to arrive at the claimed genus
- others, including predictability of the technology

Applicants submit that when the above factors are taken into consideration, there is no motivation provided in Skulnick to select the claimed genus.

1. Because the genus of Skulnick encompasses thousands of compounds, there is no motivation to select the claimed genus

Skulnick describes three generic structures, formulas Ia, Ib and Ic. For formula Ib, the formula encompassing the compounds of the present invention, there are 6 radicals, each radical defined by 2 to 7 substituents. Accordingly, there are at least 4,480 ($4 \times 2 \times 20 \times 2 \times 2 \times 7 = 4480$) different compounds encompassed by formula Ib, not including the additional compounds encompassed by substituents such as lower-alkylimino, lower-acylimino, loweralkyl, lower-alkoxylower-alkyl and lower-alkylthiolower-alkyl. For example, “loweralkyl” is defined in column 4, lines 16-19 as:

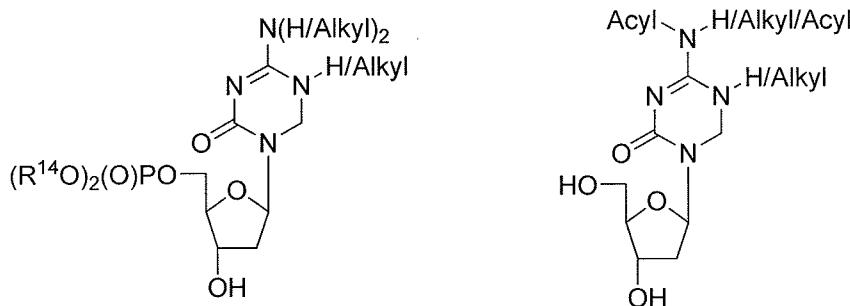
The term “lower alkyl” is employed in its usual sense as meaning alkyl of from 1 to 4 carbon atoms, inclusive, such as methyl, ethyl, propyl, butyl and isomeric forms thereof.

Accordingly, “loweralkyl” includes at least 8 (methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl) different substituents when the isomeric forms are included, and a substituent such as “lower-alkylthiolower-alkyl” includes at least 64 different substituents ($8 \times 8 = 64$). Thus, the 2 substituents for R’ would actually be 9 substituents, for example, and the 6 substituents of R would be at

least 76 substituents. Incorporating the actual number of substituents into the calculation would clearly provide a substantially greater number of compounds encompassed by the generic formula Ib of Skulnick than the 4,480 calculated above. Accordingly, Applicants submit that the size of the genus in Skulnick is substantially large that there is no motivation for one of skill in the art to select the claimed genus.

2. Because Skulnick expressly teaches 2-oxo-4-amino compounds without an N⁴-acyl group and without a 5'-phosphonate group, there is no motivation to select the claimed genus

The amended claims are drawn to compounds such as N⁴-acyl compounds and 5'-phosphonate compounds:



In contrast, the compounds expressly taught by Skulnick do not include compounds with any acyl group, much less an N⁴-acyl group, or any phosphonate group, much less a 5'-phosphonate group. In fact, the 2,4-dione and 2-thiocarbonyl-4-oxo compounds of Skulnick do not even have an N⁴ nitrogen that can be substituted with an acyl group. Thus, because the express teachings in Skulnick do not provide a particular reason to select the claimed genus or a compound within the claimed genus, Applicants submit that the specific compounds of Skulnick do not provide the requisite motivation to select the claimed genus.

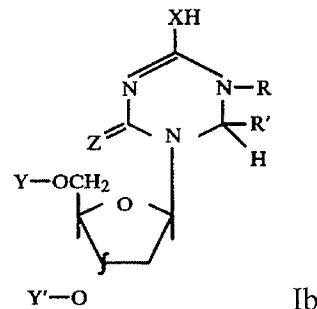
3. Because there is no teaching of structural similarity of the compounds of Skulnick to the compounds of the claimed genus, there is no motivation to select the claimed genus

As discussed above, the Examiner must provide some motivation for modifying the known compound to arrive at the claimed compound:

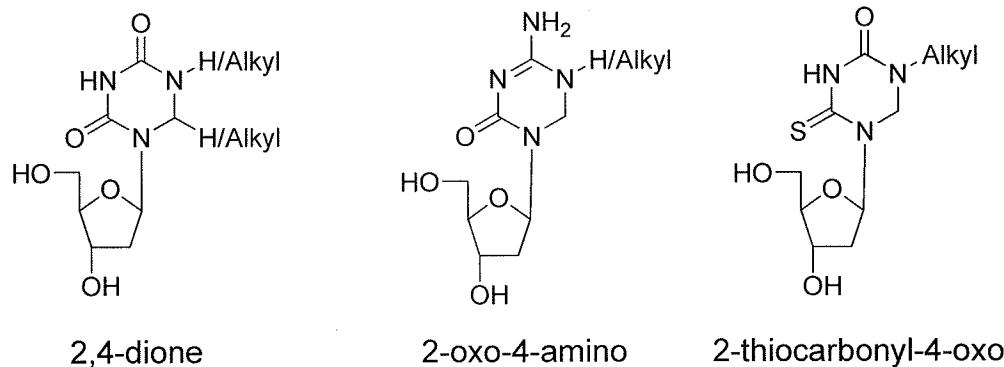
Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound ... in a particular way to achieve the claimed compound. *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 533 F.3d 1353, 87 USPQ2d 1452, 1455 (Fed. Cir. 2008). (Emphasis added.)

Applicants submit that there is no such motivation in Skulnick to modify the Skulnick compounds and arrive at the claimed genus.

Skulnick describes compounds of formula Ib for the treatment of DNA viruses (column 2, lines 20-69):



wherein Y can be H or phosphono, Y' is H, X can be imino, lower-alkylimino or lower-acylimino, Z is O, R is H or lower-alkyl and R' is H. Of the thousands of possible compounds encompassed by the Skulnick genus, Skulnick actually prepares only the following 3 classes of compounds (see Examples):



Of the Skulnick compounds, the 2-oxo-4-amino compounds (shown above in a tautomeric form of the compounds in the Examples) are closest to the compounds of the present invention.

In order to support a *prima facie* case of obviousness, the Examiner must point to some motivation in Skulnick to modify the 2-oxo-4-amino compounds and arrive at the N^4 -acyl or 5'-phosphonate compounds of the instantly amended claims. Applicants submit that there is no motivation in Skulnick or elsewhere, to make such a modification because there is no description of the use of an acyl group at the N^4 -position, or any other position, of the Skulnick compounds other than in the disclosure of the genus. Likewise, there is no description of the use of a phosphonate group at the 5'-position, or any other position, of the Skulnick compounds other than in the disclosure of the genus. Moreover, there is no disclosure in Skulnick of the advantages that such modifications would impart to the claimed compounds. Thus, there is no motivation provided in Skulnick to modify the 2-oxo-4-amino compounds and arrive at the compounds of the amended claims.

Accordingly, Skulnick provides motivation to prepare 2,4-diones, 2-oxo-4-amino and 2-thiocarbonyl-4-oxo nucleosides, but not the 2'-deoxy-5,6-dihydro-5-azacytidine compounds of the present invention having an N⁴-acyl group or a 5'-phosphonate group.

4. Because the chemical arts are unpredictable, there is no motivation to select the claimed genus

As is generally accepted, the chemical arts are unpredictable. Thus, starting from the compounds of Skulnick, there is no expectation that the compounds of the instantly amended claims would be useful for the treatment of viruses, without some motivation to prepare the instantly claimed compounds.

Because Skulnick fails to provide the necessary motivation to select the substituents of formula Ib, or modify the 2-oxo-4-amino compounds of Example 4, and arrive at the compounds of the present invention, the amended claims are not obvious under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

III. OBVIOUSNESS REJECTION OVER SKULNICK AND CULLIS

Claims 12-15 have been rejected under 35 USC § 103(a) as allegedly being obvious over Skulnick in view of Cullis. Applicants respectfully traverse the rejection in view of the comments below.

As noted above, Skulnick provides a large generic that encompasses the claimed genus, but provides no motivation for selecting the claimed genus. The Examiner relies on Cullis to describe an amphiphilic species and a dendrimeric polyamine. However, Cullis does not provide the failings of Skulnick, namely a 2'-deoxy-5,6-dihydro-5-aza-cytidine compound having either an N⁴-acyl group or a 5'-phosphonate group, for example. Thus, Applicants submit that the amended claims are not obvious over the combination of Skulnick and Cullis under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

IV. OBVIOUSNESS REJECTION OVER SKULNICK AND MCGUIGAN

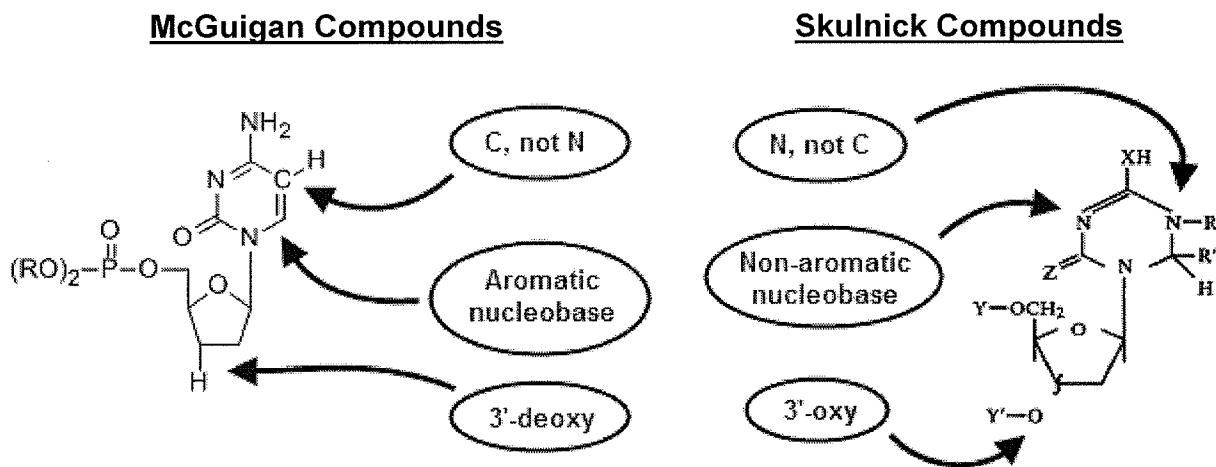
Claims 10 and 11 have been rejected under 35 USC § 103(a) as allegedly being obvious over Skulnick in view of McGuigan. Applicants respectfully traverse the rejection in view of the comments below.

As noted above, Skulnick provides a large generic that encompasses the claimed genus, but provides no motivation for selecting the claimed genus drawn to N⁴-acyl and 5'-phosphonate compounds of the 2'-deoxy-5,6-dihydro-5-azacytidine structure. The Examiner points to McGuigan as

describing phosphate derivatives of AZT, alleging that it would have been obvious to modify the compounds of Skulnick with the phosphate group of McGuigan. Applicants respectfully disagree because Skulnick does not describe 5'-phosphate compounds, and because there is no motivation to combine the McGuigan with Skulnick.

As discussed above, Skulnick provides generic formula Ib that describes the 5'-position as optionally including a phosphono group. Of the Skulnick compounds actually prepared, however, not a single compound actually includes a phosphono group in the 5'-position, or in any other position of the nucleoside. Thus, Skulnick fails to provide a description of a 2'-deoxy-5,6-dihydro-5-azacytidine compound having a phosphonate group at the 5'-position.

Moreover, McGuigan does not provide this failing of Skulnick. McGuigan describes 2',3'-dideoxy-cytidine compounds having a phosphonate at the 5'-position. The McGuigan compounds, however, differ from the Skulnick compounds by (1) having a carbon at the 5-position of the cytosine ring rather than the 5-aza of Skulnick, (2) the cytosine ring is aromatic rather than the non-aromatic 5,6-dihydro-5-azacytosine ring of Skulnick; and (3) the sugar moiety is missing the 3'-hydroxy group of the compounds of Skulnick:



In view of these differences, Applicants submit that there is insufficient structural similarity between the compounds of Skulnick and McGuigan to motivate one of skill in the art to use the phosphate group of McGuigan on a compound of Skulnick.

As Skulnick fails to describe any compound having a phosphate group, and the differences in the compounds of Skulnick and McGuigan, Applicants submit that the amended claims

are not obvious over the combination of Skulnick and McGuigan under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

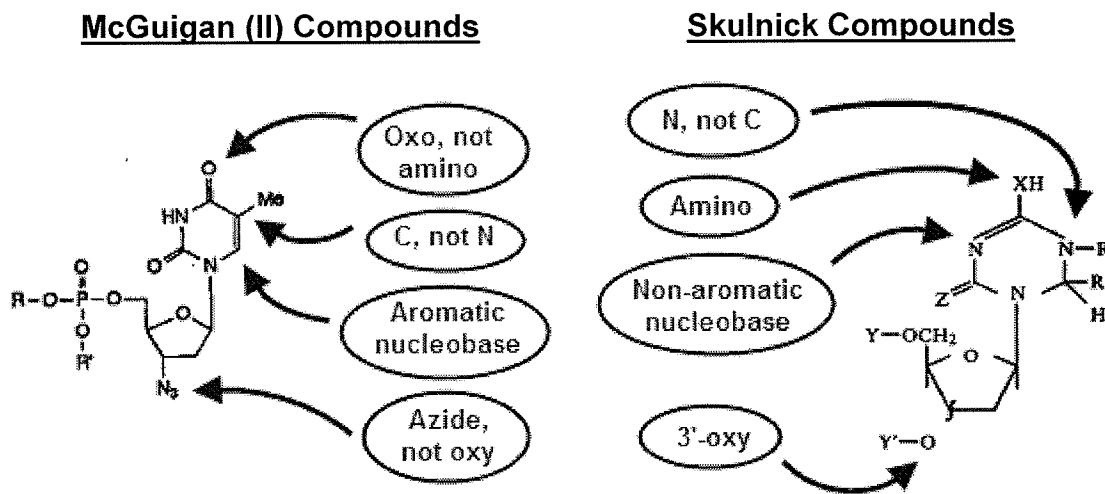
V. OBVIOUSNESS REJECTION OVER SKULNICK AND MCGUIGAN II

Claims 8 and 9 have been rejected under 35 USC § 103(a) as allegedly being obvious over Skulnick in view of McGuigan (II). Applicants respectfully traverse the rejection in view of the comments below.

As noted above, Skulnick provides a large generic that encompasses the claimed genus, but provides no motivation for selecting the claimed genus drawn to N⁴-acyl and 5'-phosphonate compounds of the 2'-deoxy-5,6-dihydro-5-azacytidine structure. The Examiner points to McGuigan (II) as describing aryl phosphate derivatives of AZT, alleging that it would have been obvious to modify the compounds of Skulnick with the phosphate group of McGuigan (II). Applicants respectfully disagree because Skulnick does not describe 5'-phosphate compounds, and because there is no motivation to combine the McGuigan (II) with Skulnick.

As discussed above, Skulnick provides generic formula Ib that describes the 5'-position as optionally including a phosphono group. Of the Skulnick compounds actually prepared, not a single compound actually includes a phosphono group in the 5'-position, or in any other position of nucleoside. Thus, Skulnick fails to provide a description of a 2'-deoxy-5,6-dihydro-5-azacytidine compound having a phosphonate group at the 5'-position.

Moreover, McGuigan (II) does not provide this failing of Skulnick. McGuigan (II) does describe AZT having a phosphonate at the 5'-position. The McGuigan (II) compounds, however, differ from the Skulnick compounds by (1) having a carbon at the 5-position of the cytosine ring rather than the 5-aza of Skulnick, (2) the cytosine ring is aromatic rather than the non-aromatic 5,6-dihydro-5-azacytosine ring of Skulnick; (3) the sugar moiety is missing the 3'-oxy group of the compounds of Skulnick; and (4) having a 4-oxo group rather than the 4-amino group of the Skulnick compounds:



In view of these differences, Applicants submit that there is insufficient structural similarity between the compounds of Skulnick and McGuigan (II) to motivate one of skill in the art to use the phosphate group of McGuigan (II) on a compound of Skulnick.

As Skulnick fails to describe any compound having a phosphate group, and the differences in the compounds of Skulnick and McGuigan (II), Applicants submit that the amended claims are not obvious over the combination of Skulnick and McGuigan (II) under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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